Many Clinical Laboratories Performing Next-Generation Sequencing Have No Future Plans to Migrate to the Most Recent Human Reference Genome Build (GRCh38)

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Describe role of Submitting/Presenting Trainee in this project (limit 150 words): The submitting/presenting trainee designed the survey for this study, coordinated its distribution and analyzed all results.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background: Analysis of clinical next-generation sequencing (NGS) data requires the Human Reference Genome (HRG) for alignment. Build GRCh38 was released in December 2013 and resolved ~1,000 issues from GRCh37, including erroneous calls within clinically-relevant genes.

Objectives/Goal: Despite this new release becoming available over seven years ago, most clinical laboratories continue to use build GRCh37. We were interested to learn other clinical laboratory's plans for migration to GRCh38, including their proposed timelines and related concerns; therefore, we conducted a survey to define the current landscape of genome alignment in clinical NGS.

Methods/Design: Seventy-one clinical laboratories performing constitutional NGS testing were invited to participate in an unvalidated online survey to understand general laboratory characteristics as well as motivation for migrating or not migrating to GRCh38.

Results: Thirty-three of 71 laboratories responded (46%), 28 of which met criteria for downstream analyses. The overwhelming majority of laboratories (26; 93%) reported using build GRCh37, whereas only 2 laboratories (7%) said that they had already migrated to GRCh38. Surprisingly, 15 of the 26 laboratories who had not yet migrated indicated that they had no future plans to migrate to GRCh38. The most common factors affecting migration for these 26 laboratories were that the benefit of GRCh38 did not outweigh the time and monetary cost to migrate (14; 54%) and, also, that there were insufficient staff available to facilitate the migration (12; 46%).

Conclusions: Clinical laboratories are divided about migrating to build GRCh38 due to limited resources. This is expected to change within the next one to two years as a variety of large-scale databases (i.e. GnomAD, Genomics England, ClinVar, HGMD, etc.) have already transitioned. We conclude that increased awareness of clinically-relevant variation that may be missed by NGS pipelines using build GRCh37 is needed, and orthogonal bioinformatics approaches to reduce the likelihood of missing such variants should be considered.